Section III. (Remarks)

Amendment of the Specification.

In response to the examiner's request for amendment of the specification at page 1, line 1 to "include a specific reference to the priority application PCT/DE00/02589 for which benefit is sought and the status of the instant application is a 371" (page 3, paragraph 3 of the March 13, 2006 Office Action), it is to be noted that such specific reference has already been included in the specification by operation of the Preliminary Amendment filed February 5, 2002 in the present application.

Such Preliminary Amendment at page 2 thereof contained the following:

"Please insert on page 1, between the title of the application and the first paragraph, the following new paragraph:

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is filed under the provisions of 35 USC §371 and claims the priority of International Patent Application No. PCT/DE00/02589 filed August 2, 2000, which in turn claims priority of German Patent Application No. 199 37 264.0 filed August 6, 1999."

Accordingly, the specific reference requested by the examiner is already present in the application, and the examiner's acknowledgement of same is respectfully requested.

The specification also has been amended at page 2, second paragraph, to insert the deposit number (DSM deposit number ACC 2142), and reference to U.S. Patent 5,643,759 (of record) wherein such bimAbHRS-3/A9 antibody is described. No new matter (35 USC 132) has been added.

Submission of English Translation of German Priority Application

In response to the examiner's request for English translation of the priority document (German application no. 19937264) and to the inquiry as to whether the foreign priority document provides written description for the instant claims, applicant has ordered an English translation of the

German priority document, and same will be submitted to the USPTO upon its receipt by the undersigned attorney, to perfect the priority claim to German application no. 19937264.

Applicant hereby affirmatively states that the subject matter of the pending claims is fully entitled to the August 6, 1999 priority of German application no. 19937264, as will be independently verifiable by the examiner upon the near-term submission of the English translation of such German priority application.

In connection with the German references of the IDS filed June 7, 2002, the Examiner has stated that references AC, AD and AE of the IDS have not been considered, because English translations have not been provided. In response, it is noted that reference AC corresponds to U.S. Patent 5,643,795; reference AD corresponds to U.S. Patent 6,294,167; and reference AE relates to a monovalent anti-CD30 single-chain F_V. The examiner therefore is requested to take cognizance of such U.S. Patent counterparts and subject matter.

In response to the examiner's requirement for designation of trademarks in the application, the specification has been amended at page 9 to identify the analytical instrument as a FACSCAN flow cytometer. Applicant is unaware of any other trademarks in the application.

Amendment of Claims in Response to Examiner's Objections

In response to the examiner's objections:

- Claims 2 and 17 have been amended to set forth the full name of "NK cells" as "natural killer cells."
- Claim 19 has been amended to recite "a VH domain of an anti-CD16 antibody."

Although objected to as such, the specific objection to claim 5 (paragraph 6 of the March 13, 2006 Office Action) was not particularized, so that the objection to claim 5 appears to involve an inadvertent typographical error in the Office Action.

Response to 35 USC 112, Second Paragraph Rejections

In response to the examiner's rejections under 35 U.S.C. 112,

A) In claims 1, 2, 3, 15 the recitations of "receptor" and "surface protein" have been canceled to make clear that the claims are drawn to CD16/CD30 themselves as suggested by the Examiner.

B) In claim 5 the recitation of the plasmid has been corrected, as supported at page 4, paragraph 4.

C) Attached in Appendix A hereof is a deposit receipt for the deposit of the pKID16-30 expression vector as DSM 12960 under the terms of the Budapest Treaty, as to which it is hereby stated by the undersigned attorney that this expression vector has been deposited with the DSMZ under the Budapest Treaty and that the expression vector will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, and that the deposit will be maintained in such public depository for a period of 30 years after the date of deposit, 5 years after the last request for a sample, or for the enforceable life of the patent, whichever is longer.

Such rejections therefore are overcome.

Response to 35 USC 102 Rejections

In response to the Examiner's rejection based on 35 U.S.C. 102 and the citation of Arndt et al., it is noted that Arndt was published after the priority date. Based on such priority date and the English translation of the priority document to be filed, Arndt et al. is not competent prior art against claims 1-6, 15 and 19, and such rejection therefore is properly withdrawn.

The Examiner has rejected claims 1-5 and 15 as being anticipated by Hartmann et al. Hartmann et al. disclose bispecific monoclonal antibodies comprising constant domains (see abstract). The claims have been amended to recite a F_V antibody which does not comprise constant domains. (support for the added claim recitals of "variable domains ... but not constant domains" and "inducing a regression of Hodgkin's disease" is found at page 2, 2nd and 4th paragraphs).

The examiner has pointed out that Hartmann et al teach that side effects such as HAMAs can be resolved by using less immunogenic bispecific single-chain antibodies. However, Hartmann et al. do not disclose anti-CD16/CD30 single-chain antibodies. Therefore, this rejection is properly withdrawn, in application to the amended claims.

Response to 35 USC 102 Rejections

The Examiner's rejections of claims 1-5, 15 and 19 based upon 35 U.S.C. 103, as obvious in view of Hartmann et al. and Holliger et al., are based on the teachings of Hartmann et al. regarding the effect of bispecific anti-CD16/CD30 antibody in treating Hodgkin's lymphoma, and the teachings of Holliger et al. providing methods of making diabodies without Fc region, as to which the examiner has contended the skilled person would have had a reasonable expectation of producing anti-CD16/CD30 F_V construct.

The claims as now amended are limited to anti-CD16/CD30 F_V antibody constructs "including a regression of Hodgkins's disease *in vivo*" (support for the added claim recitals of "variable domains ... but not constant domains" and "inducing a regression of Hodgkin's disease" is found at page 2, 2nd and 4th paragraphs).

Hartmann et al. teach the tumoricidal potential of a specific anti-CD16/CD30 IgG antibody. Further, Hartmann et al. suspect that the development of HAMA could be prevented by the construction of single-chain antibodies, such as diabodies, which would also result in a reduction of costs (page 2046). However, Hartman et al. do not disclose or teach that single-chain antibodies are capable of inducing a regression of Hodgkin's disease *in vivo*. Hartmann et al. only refer to other bispecific IgG antibodies (page 2044, 1st paragraph of "Discussion"), but do not indicate that a single-chain antibody is capable for immune recruitment *in vivo*.

Hollinger et al. do not overcome the deficiencies of Hartmann et al. Holliger et al. teach bispecific single-chain constructs of the so-called "diabody"-format. Holliger et al. disclose that constructs having variable domains specific for anti-2-phenoyloxazol-5-one (phOx) and anti-hen egg lysozyme (HEL) bind to the respective antigens *in vitro*. Holliger et al. neither teach that the constructs are capable of binding their antigens *in vivo* nor that they show any immunotherapeutic effect. Above all, Holliger et al. do not disclose any diabody binding to a tumor-associated antigen. Therefore, Holliger et al. do not teach or suggest that a diabody having binding sites for CD16/CD30 may exhibit a cytotoxic activity. Holliger et al. mainly suspect that diabodies "should facilitate penetration of tumors and clearance from the serum," but do not teach any therapeutic, in particular cytotoxic, activity of the diabodies.

Therefore, it was not predictable from Hartmann et al. in view of Holliger et al. that a F_V antibody construct having variable domains for CD16 and CD30 is capable of inducing a regression of Hodgkin's disease *in vivo*. At the time the invention was made it was not known that a diabody is

capable for immune recruitment by targeting and activating natural killer cells *in vivo* and neither Hartman et al. nor Holliger et al. provide any evidence suggesting that an anti-CD16/CD30 F_V antibody would be therapeutically effective. Thus, a skilled person could not have had any reasonable expectation of success that an anti-CD16/CD30 F_V antibody construct is capable of inducing a regression of Hodgkin's disease.

Diabodies (approx. 60 kD) as disclosed by Holliger et al. are smaller than IgG-antibodies (approx. 150 kD) as disclosed by Hartmann et al. Thus, diabodies are cleared much faster from the serum than IgG-antibodies. Arndt et al. reports that the half-life time of diabodies according to the invention was about 6h, whereas the half-life time of the IgG-antibodies according to Hartmann et al. was about 107h (see Arndt et al., page 2567, 2nd paragraph from the bottom). Thus, the diabodies have to elicit their cytotoxic activity during a much shorter time than the IgG-antibodies. From this it could not be reasonably expected that a treatment with diabodies (a) induces a regression of tumors *in vivo* and (b) the diabodies having at the same time a therapeutic efficiency comparable with that of the IgG-antibody (see Fig. 4 of Arndt et al.) which is required for a therapeutic treatment and was not derivable from Holliger et al. or Hartmann et al., because neither Hartmann et al. nor Holliger et al. teach or suggest that a F_V antibody construct is sufficiently cytotoxic and capable to elicit a therapeutic effect, due to its short half-life.

Moreover, blood cells are negatively charged *in vivo* to prevent agglomeration of the cells in the blood stream. Neither Holliger et al. nor Hartmann et al. teach or suggest whether the small single-chain F_V constructs are capable of binding two negatively charged cells with the same molecule at the same time.

Regarding newly added claim 22 it could not be expected from Holliger et al. and Hartmann et al. that a F_V antibody construct according to the present invention elicits a several times higher cytotoxicity than the bimAbHRS-3/A9 IgG-antibody of Hartmann et al. *in vitro*. While the application of the IgG-antibody of Hartmann et al. results in a lysis of 25% of the cells, the F_V-construct according to the invention achieved a lysis of 75% of the cells, although the concentration of the IgG-antibody (4µg/ml) was four times higher than the concentration of the F_V-antibody according to the invention (1µg/ml) (see Fig. 3 of the application)!

Neither Hartmann et al. nor Holliger et al. teach or suggest that a F_V antibody construct may have a higher cytotoxicity than the IgG-antibody taught by Hartmann et al. However, it turned out that

the higher specific cytotoxicity is important for showing a therapeutic effect *in vivo* due to the very short half-life time of F_V antibody constructs *in vivo*.

For all these reasons, claims 1-5, 15 and 19, as well as new claim 22, are patentable over the art and in condition for allowance.

Fee Payable for Added Claim 22

The addition of new claim 22 herein increases the number of total claims beyond the number for which payment was previously made, by one. Accordingly, an added claims fee of $25 is payable. A Credit Card Authorization Form authorizing charging of the credit card specified therein in such amount, is enclosed and submitted herewith.

Authorization also is hereby given to charge the amount of any deficiency or any amount additionally payable in connection with the filing and entry of this response, to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

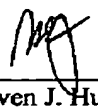
CONCLUSION

Based on the foregoing, the Examiner is requested to allow claims 1-6, 15, 19 and 22.

If any additional issues remain, the Examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss same, in order that same may be promptly resolved, to facilitate issue of a patent on the present application at an early date.

**INTELLECTUAL PROPERTY/
TECHNOLOGY LAW
Phone: (919) 419-9350
Fax: (919) 419-9354
Attorney File No.: 4121-135**

Respectfully submitted,



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Attorney for Applicants

Appendix A

BUDAPESTER VERTRAG ÜBER DIE INTERNATIONALE ANERKENNUNG DER HINTERLEGUNG VON MIKROORGANISMEN FÜR DIE ZWECKE VON PATENTVERFAHREN

INTERNATIONALES FORMBLATT

Deutsches
Krebsforschungszentrum
AG Rekombinante Antikörper
Abt. D0500
Im Neuenheimer Feld 280
69120 Heidelberg

EMPFANGSBESTÄTIGUNG BEI ERSTHINTERLEGUNG, ausgestellt gemäß Regel 7.1 von der unten angegebenen INTERNATIONALEN HINTERLEGUNGSSTELLE

I. KENNZEICHNUNG DES MIKROORGANISMUS

Vom HINTERLEGER zugeteiltes Bezugszeichen:
pKID16-30

Von der INTERNATIONALEN HINTERLEGUNGSSTELLE zugeteilte EINGANGSNUMMER:
DSM 12960

II. WISSENSCHAFTLICHE BESCHREIBUNG UND/ODER VORGESCHLAGENE TAXONOMISCHE BEZEICHNUNG

Mit dem unter I. bezeichneten Mikroorganismus wurde

(X) eine wissenschaftliche Beschreibung
(X) eine vorgeschlagene taxonomische Bezeichnung

eingereicht.
(Zutreffendes ankreuzen).

III. EINGANG UND ANNAHME

Diese Internationale Hinterlegungsstelle nimmt den unter I bezeichneten Mikroorganismus an, der bei ihr am 1999-07-29 (Datum der Ersthinterlegung)[1] eingegangen ist.

IV. EINGANG DES ANTRAGS AUF UMWANDLUNG

Der unter I bezeichnete Mikroorganismus ist bei dieser Internationalen Hinterlegungsstelle am eingegangen (Datum der Ersthinterlegung) und ein Antrag auf Umwandlung dieser Ersthinterlegung in eine Hinterlegung gemäß Budapester Vertrag ist am eingegangen (Datum des Eingangs des Antrags auf Umwandlung).

V. INTERNATIONALE HINTERLEGUNGSSTELLE

Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH

Anschrift: Mascheroder Weg 1b
D-38124 Braunschweig

Unterschrift(en) der zur Vertretung der internationalen Hinterlegungsstelle befugten Person(en) oder des (der) von ihr ermächtigten Bediensteten:

U. Weiks

Datum: 1999-08-03

[1] Falls Regel 6.4 Buchstabe d zutrifft, ist dies der Zeitpunkt, zu dem der Status einer internationalen Hinterlegungsstelle erworben worden ist.

Formblatt DSMZ-BP/4 (einzige Seite) 0196